REMARKS

Reconsideration and allowance of this application are respectfully requested in light of the following remarks.

Claim Status

Claims 1-20 were presented in the originally filed application. Claims 14-20 are withdrawn. Claims 1-13 are pending. No new matter was added.

Discussion

Claims 1-13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,582,941 (Yokochi), U.S. Patent No. 6,509,178 (Tanaka), EP 0 113 183 (Carson), and Bajpai. Applicant traverses.

As stated in the previous office action, the combination of Yokochi, Tanaka, Carson, and Bajpai fail to establish a prima facie case of obviousness. MPEP §2143 "Basic Requirements of a *Prima Facie* Case of Obviousness" states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine references teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all claim limitations.

Regarding the third criterion, the court has stated that "to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Applicant contends that none of the prior art references, Yokochi, Tanaka, Carson, and Bajpai, alone or in combination, teach, suggest, or provide a motivation for making an article of manufacture with all of the claim elements from independent claims 1 and 13. More specifically, Applicant contends that none of the prior art references, alone or in combination, teach, suggest or provide a motivation for a method for cultivating microorganisms of the order *Thraustochytriales*, characterized in that the microorganisms are cultivated in a fermentation medium containing $CaCO_3$ as an essential (or exclusive) means for pH value stabilization, where content of $CaCO_3$, in the fermentation medium is 3 to 15 g/l.

The crux of the instant invention is that in prior art fermentation processes, strong pH variations in the course of the cultivation occur as a result of the appearance of metabolic products and/or the consumption of individual media components which require permanent pH control. (Specification, Page 2, Lines 26-33). In contrast, the present invention makes use of a fermentation medium having a calcium carbonate content in the range of 3-15 g/L. (Specification, Page 7, Lines 19-22). This ensures stabilization of the pH value of the fermentation medium in the range of pH 5-7, which has been proven to be the optimum range fort he fermentation of Thraustochytriales (Specification, Page 8, Lines 26-28) so that no further regulation of the pH value is required. (Specification, Page 5, Lines 3-8).

In sum, the rejection goes like this: Yokochi is cited for the purpose of disclosing cultivation of Schizochytrium Genus SR21 for the production of DHA and DPA. (Yokochi, Column 18, Lines 14-23). As noted by the Examiner, Yokochi makes no reference to the use of calcium carbonate as a material for the adjustment of pH levels in the fermentation medium. The Examiner then cites Tanaka for the purpose of disclosing cultivation of Ulenia sp. strain SAM 2179 for the production of DHA and DPA. (Tanaka, Column 2, Lines 63-65). As noted by the Examiner, Tanaka makes no reference to the use of calcium

carbonate as a material for the adjustment of pH levels in the fermentation medium. The Examiner then cites Carson as disclosing the use of calcium carbonate in the liquid phase of a fermentation mixture. (Carson, Page 9, Lines 7-11). The Examiner also cites the reference by Bajpai as disclosing the cultivation of *Thraustochytrium aureum*, in a culture medium containing calcium carbonate.

Looking first to Bajpai, this reference relates to studies on the optimization of DHA production by Thraustochytrium aureum. According to these studies, the content of lipids and DHA in the obtained biomass is optimal when the initial pH value of the culture medium is 6. (See: Abstract, Figure 1, Page 510, Column 2, 2nd full Paragraph). In this context, however, it must be noted that in these studies the cells had been cultured for a period of six days in a weakly buffered medium prior to harvesting. (Page 509, Column 2, 3rd full Paragraph and 5th full Paragraph). There is absolutely no indication provided within Bajpai that the culture medium was ever changed during the course of the cultivation. Hence, the above mentioned effects occurred (i.e., metabolic products appeared and individual media components were consumed) resulting in a significant decrease of the pH value of the culture medium and, as a consequence, in a substantial decrease in the growth of the microorganisms. In

this respect, reference is made to Table 1 of the instant application which illustrates that the pH value of a customary, but unbuffered culture medium, sharply decreases from an initial value of 6 to < 2 (Medium 1.1) after a cultivation period of 96 hours (i.e. 4 days).

A person skilled in the art knows that the pH value sharply decreases in the course of the fermentation process and since Bajpai et al refrain from buffering the culture medium, it is clear that Bajpai et al consider such a decrease of the pH value to be necessary, or at least not detrimental, to achieving an optimization of the DHA production.

Additionally, while it is acknowledged that the culture medium used by Bajpai et al contains calcium carbonate, the amount utilized (0.1 g/L) is not sufficient to stabilize the pH value. This fact is clearly demonstrated in Table 1 of the instant application which demonstrates that 1 g/L of calcium carbonate contained in Medium 1.2 is insufficient to ensure buffering of the culture medium. Hence, it is abundantly clear that Bajpai did not make use of calcium carbonate as a pH stabilizer.

In summary, Bajpai clearly teaches that the pH value does not have to be kept within a range of 5-7, but instead is permitted to decrease far below pH 6 during cultivation. Consequently, Bajpai et al does not suggest or even hint at the cultivation of Thraustochytriales in the presence of 3 - 15 g/L calcium carbonate as the essential means for pH value stabilization.

Looking now to EP 0 113 183 (Carson), we see that this reference relates to the control of the pH value of a mixture in which alcoholic fermentation occurs. More specifically, this reference relates to the fermentation of yeasts. The pH value of this mixture is stabilized in the range of pH 3-8 by the addition of 0.5 - 5 g/L calcium carbonate. Thus, Carson only teaches that calcium carbonate may be used to buffer a fermentation medium and that this is beneficial as far as the particular metabolic process of alcoholic fermentation in the particular organism yeast is concerned. **However, it is to be noted that yeasts, as used for alcoholic fermentation on the one hand and Thraustochytriales on the other hand, are totally different organisms.** It must also be noted that the process of alcoholic fermentation (in which carbohydrates are metabolized to ethanol and CO_2) is totally different from the production of polyunsaturated fatty acids (PUFAs). Therefore, from the view

of an individual who is skilled in the art, it is inappropriate and inconceivable that based on the cultivation conditions disclosed in Carson, conclusions may be drawn with respect to the optimization of a completely different metabolic process in a completely different organism.

The solution sought in the instant invention is to determine conditions under which Thraustochytriales shows high and rapid glucose consumption and thus an increasing production of polyunsaturated fatty acids while avoiding acidification of the culture medium which is generally observed under these conditions. (Specification, Page 5, Lines 3-8, Page 6, Lines 6-9). **A person skill in the art would know that studies on the fermentation of yeasts, such as that described in Carson, cannot and do not provide a solution to the above problem based on the simple fact that different metabolic processes occur in yeasts.**

As to the solution to the problem sought by the instant invention, reference can be made to Example 1 (Table 1) of the instant application: When fermentation media 1.4 and 1.5 (containing 5 or 10 g/L calcium carbonate, respectively) are used, the dry biomass (DBM) content after 4 days of cultivation is about 50 g/L, while fermentation in medium 1.1 (which lacks buffering with calcium carbonate) results in a dry biomass

content of only about 20 g/L. Additionally, when the culture medium is buffered in accordance with the instant invention, (media 1.4 and 1.5) the DHA/DBM content is approximately five-fold the DHA/DBM content after cultivation in unbuffered medium (media 1.1) resulting, in total, in an approximately ten-fold higher DHA content. Moreover, when media 1.4 and 1.5 are used, the space-time yield of 2.08 or 1.73 g/(L x d) and thus ten-fold the space-time yield when culture medium lacking calcium carbonate is utilized.

In order to render the instant invention obvious, a prior art document, such as Carson, must teach that culturing Thraustochytriales in a medium buffered with 3-15 g/L calcium carbonate brings about an increased glucose consumption and thus an increase of the biomass. (Specification, Page 11, Lines 1-15). **In Carson, such a teaching is lacking. Therefore the instant invention is not obvious in view of Carson.**

Looking now to Tanaka, the pH value of the culture medium for the production of DHA and DPA by Ulkenia is adjusted to pH 4, preferably. (Column 4, Lines 50-54, Examples 1 and 2). Also looking to Yokochi which teaches one may increase the PUFA production of Schizochytrium by adjusting the pH value to pH 4-4.5 (Column 11, Lines 17-27). Tanaka and Yokochi each mention

broader pH ranges for the used culture medium as well. (Tanaka, pH 3-8, Column 4, Lines 50-54) and (Yokochi, pH 3.5-6, Column 11, Lines 17-27). However, these statements relate to the pH value of the beginning of the cultivation. As mentioned above, this initial pH value significantly decreases as the cultivation progresses. This is the reason, according to both references, the pH value of the medium has to be adjusted during the course of cultivation to pH 4 through the use of 10% sodium hydroxide. (Tanaka, Examples 1 and 2, Yokochi, Example 5). Neither the two references just mentioned, nor the two previous references, teaches that the pH value of the medium must be maintained at a constant pH5-7 during the entire cultivation period.

Additionally, Applicant respectfully disagrees with the Examiner's statements in which he claims that, in the fermentation of Thraustochytriales, buffering the medium with calcium carbonate would not provide any advantages over buffering with conventional stabilization means. Apart from the obvious over-simplification of the fermentation process (Page 2, Lines 30-33), which results in a reduction of costs, the method of the present invention ensures a significant increase in biomass compared with the fermentation of Thraustochytriales using conventional buffering agents. The Examiner denies this fact and refers to both Tanaka and Yokochi stating that Yokochi

would show a similar increase in the fatty acid and DHA content when conventional culture conditions are chosen (Table 7, strain SR21), and that Tanaka would show a comparable increase in DHA production (Table 1, SAM 2179). However, these arguments are not appropriate. While according to table 7 (strain SR21) of Yokochi, the DHA content per liter (7.2g/L) is approximately the same as obtained according to the present invention (Specification, Table 1, media 1.4 and 1.5: DHA content = 8.33 or 6.92 g/L, respectively), **the total fat content of 53.5 g/L as referred to by the Examiner is meaningless because the goal of the instant invention is not to increase the total fat content, but the content of the PUFAs**. In this context, however, it is important to note that the biomass ("amount of cell bodies") according to table 7 (39.6 g/L) is significantly lower than the biomass obtained after cultivation according to the instant invention (Specification, Table 1, media 1.4 and 1.5: DBM = 52.99 or 52.32, respectively). Additionally, comparison with the values obtained in Table 1 of Tanaka using the strain SAM 2179 (which was also used in the Examples of the instant application) shows the beneficial effects of the instant application: While according to Table 1 of Tanaka, the DHA content is 5.5g/L and the dry biomass ("dry cell weight") is 19.5 g/L, both values are much higher when cultivation is performed in accordance with the instant invention

(Specification, Table 1, Media 1.4 and 1.5: DHA content = 8.33 or 6.92 g/L, respectively; DBM content = 52.99 or 52.32, respectively). Therefore, the fermentation of Thraustochytriales, stabilization of the pH value by means of calcium carbonate leads to obvious beneficial effects.

As stated in the previous office action, the prior art reference or combination of references relied upon by the Examiner must teach or suggest all of the limitations of the claims. See *In re Zurko*, 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1467, 1478 (Fed. Cir. 1997); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art."). The teachings or suggestions, as well as the expectation of success, must come from the prior art, not applicant's disclosure. See *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). In this instance, from the information detailed above, it is clear that Yokochi, Tanaka, Carson, and Bajpai fail to teach or suggest all the limitations of Applicant's claims.

The U.S. Supreme Court recently held that rigid and mandatory application of the "teaching-suggestion-motivation," or TSM, test is incompatible with its precedents. *KSR Int'l Co.*

v. Teleflex, Inc. 127 S.Ct 1727, 1741 (2007). The Court did not, however, discard the TSM test completely; it noted that its precedents show that an invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.*

The Court held that the TSM test must be applied flexibly, and take into account a number of factors "in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed." *Id.* at 1740-41. Despite this flexibility, however, the Court stated that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the way the claimed new invention does." *Id.* "To facilitate review, this analysis should be made explicit." *Id.*

The obviousness rationale addressed in *KSR* was premised on combining elements known in the prior art. *Id.* at 1738-39. The *KSR* Court noted that obviousness cannot be proven merely by showing that the elements of a claimed device were known in the prior art; it must be shown that those of ordinary skill in the art would have had some "apparent reason to combine the known elements in the fashion claimed." *Id.* at 1741.

In the same way, when the prior art teaches away from the claimed solution, obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition. See also *Ex parte Thomas J. Whalen II, et al*, BPAI 2007-4423 (2008).

Based on *KSR v. Teleflex, Inc.* 127 S.Ct. 1727, 167 L.Ed2d 705, 2007 U.S. Lexis 4745 (2007), the obviousness question may be broken down to: Is the invention predictable based upon the prior art? *Id.* at 1740, 721.

Simply, the answer to that question is "no." Hindsight reconstruction is not permitted as the Federal Circuit has repeatedly warned that the requisite motivation to modify a reference must come from the prior art, not Applicant's specification. See *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988) ("there must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure.") Using an Applicant's disclosure as a blueprint to reconstruct the claimed invention from isolated piece of the

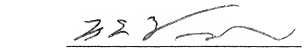
prior art contravenes the statutory mandate of section 103 of judging obviousness at the point in time when the invention was made. See *Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988).

Only hindsight reconstruction based upon the instant specification would lead the Examiner to the conclusion that the claims in the instant application are rejected under §103 as unpatentable over Yokochi, Tanaka, Carson, and Bajpai. Accordingly, the instant rejection of independent claims 1 and 13 must be removed.

In reference to claims 2-12, dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious. *Hartness Int'l, Inc. v. Simplimatic Eng'g Co., 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1831 (Fed. Cir. 1987); In re Abele, 684 F.2d 902, 910, 214 USPQ 682, 689 (CCPA 1982); see also In re Sernaker, 702 F.2d 989, 991, 217 USPQ 1, 3 (Fed. Cir. 1983).* Thus, claims 2-12 are not unpatentable over Yokochi, Tanaka, Carson, and Bajpai and should be allowed.

Reconsideration and allowance of this application is respectfully requested.

Respectfully submitted,



Blake E. Vande Garde
Attorney for Applicant
Registration No. 58,264

Customer No. 29494
Hammer & Associates, P.C.
3125 Springbank Lane
Suite G
Charlotte, NC 28226
Telephone: 704-927-0400
Facsimile: 704-927-0485
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